A short clinical trial has been made of a new drug and the results are promising enough to warrant a preliminary communication. The drug in question is marketed under the trade name of Nardil, has the generic name of phenelzine sulphate, and the chemical description of B-phenylethyl-hydrogen sulphate. It falls under the group of mono-amine oxidase (MAO) inhibitors, about which something will be said briefly below.

Dosage. Nardil is supplied in 15-mg. tablets and the usual dosage is 1 tablet 3 times daily before meals. In some cases this is increased so that the patient is given 2 tablets before breakfast and 1 tablet before each of the other two main meals of the day. The aim has been to keep patients on this dosage for 3-4 weeks, by which time the tablets can be reduced to 2 tablets daily for a varying time of another 1-4 weeks, and then stopped altogether.

Complications. Hypotension, constipation, nausea, and impotence have been reported in preliminary unpublished data supplied by the makers, but did not occur in the present series to a degree which could be labelled 'complication'. The only side-effect which was a very definite drawback in certain cases was the marked increase in tension and irritability in those cases which presented as depression with definite underlying agitation and with heightened anxiety. No renal or hepatic disorder occurred. A few patients complained of postural hypotension, but not to any marked degree, but a physician who had been taking Nardil and then took alcohol became profoundly hypotensive, possibly because of potentiation of the hypotensive effects of the drug.

CASE REPORTS

Case 1. G.H., male, 27 years. Severe depression associated with feelings of inadequacy and deepened by the death of a relative. Poor response to ECT. Four weeks after the termination of ECT, was switched to Nardil and on the second day of treatment noted an almost complete lifting of the depression. Has remained well.

Case 2. B.M., male, 56 years. Moderate to severe depression for over a year, with great exhaustion, centering around his broken marriage. Has been on various 'tonics' and had had much psychotherapy. Within a week of taking Nardil he returned to activity and his usual euphoria. Has remained well.

Case 3. E.C., male, 74 years. For 2 years depressed and exhausted and unable to leave home or to play the piano (his main source of enjoyment). On the second day on Nardil he rang up excitedly to say he could now practice on the piano for the first time for 2 years. Has remained well.

Case 4. P.V., male, 60 years. A life-long obsessional with many rituals and great anxiety, but with depression only secondary to the difficulties occasioned by compulsive actions of his counting, repeating of names, etc. Nardil made him over-active and he found himself in a whirl of obsessional rituals. Unsuccessful.

Case 5. S.F., female, 76 years. Numerous hypochondriacal fears. Lonely and almost blind. Nardil increased her anxiety about herself. Unsuccessful.

Case 6. M.V., female, 60 years. Recurrent bouts of depression with great agitation. Has responded on several occasions to ECT; no response to Nardil, but discontinued taking the drug after only 7 days. Unsuccessful.

Case 7. M.G., female, 56 years. Involutional depression in active, intelligent woman. No previous breakdowns. Main complaints were of depression, asthenia, and insomnia. Responded well after first week on Nardil. Has remained well.

Case 8. A.B., male, 35 years. Long depressive illness in a man who had enough money to make work unnecessary. Slowly withdrew from the world and found attempts at any kind of activity, social or recreative, more and more difficult. Responded

moderately well to ECT, but soon began to revert to the old condition until given Nardil. Has remained well.

Case 9. J.L., female, 48 years. Severe reactive depression after death of a relative. Did not respond to Imipramine, but is doing well on Nardil.

Case 10. O.B., male, 35 years. Recurrent episodes of depression in serious, shy man without obvious external stresses. Various supportive treatments failed, but within a week of taking Nardil he made a remarkable recovery. Has remained well.

Case 11. L.P., female, 35 years. Reactive depression after death of her father with great feelings of guilt concerning incestuous affair in childhood. Nardil made her over-anxious and distraught. Unsuccessful.

Case 12. D.T., female, 33 years. Over-protected, anxious woman, with 2 previous breakdowns on threat of loss of security (marriage difficulties). Nardil produced great anxiety and florid psychosomatic symptoms. Unsuccessful.

Case 13. M.G., female, 56 years. Two previous depressive episodes in a woman with obsessional phobias of having harmed others. Did quite well on ECT, but made a further definite improvement on Nardil almost at once. Remains well.

Case 14. I.T., female, 26 years. Marked anxiety with morbid hypochondriacal ruminations for years. Temporarily helped by ECT, but not materially improved by Nardil. Unsuccessful.

Case 15. M.M., female, 34 years. Depression related to numerous operations on back and feet. Great asthenia and depression. Remains a dependant and inadequate person but is no longer depressed when taking Nardil. Successful.

These 15 cases can be divided into the following categories and considered from the viewpoint of satisfactory and unsatisfactory results:

Depression	*Satisfactory*	*Unsatisfactory*
Cyclothymic	2	1
Hypochondriacal	—	2
Reactive	5	3
Involutional	2	—
Total	9	6

The number of cases studied is too small to give significant percentage results, but several points arise. Firstly, the results in a number of cases were dramatic and sustained and, in my opinion, could not possibly be due to suggestion or coincidental recovery. Secondly, there is no doubt that agitated states and conditions with much tension and anxiety are made worse and the patients complain of a pressure of energy within themselves which is uncomfortable and frightening. Furthermore, the 2 hypochondriacal cases did not respond, but with the well-known malign prognosis in these obsessive depressed cases one is not at all surprised. Thirdly, the sense of well-being induced by Nardil may be different to that induced by amphetamine or methylphenidate (Ritalin), according to 4 patients who have used all 3 drugs; these patients said Nardil gave them a sense of calm assurance while the two latter drugs gave them a sense of unreality with their increased energy. Against this my own experience can be cited: On 3 occasions (without, however, having been depressed) I took a 15-mg. tablet of Nardil with a resultant feeling of detached alertness verging on a feeling of unreality for several hours. This was not a particularly pleasant feeling and not one which I wish to repeat. There is no doubt that the drug had a very definite action and this comment is made to make clear that it should not be used for its euphorizing effect in *normal* people. Finally, some of the failures were due to the patient refusing to continue with the drug after being on it only a few days without any apparent beneficial effects, so that it is possible that there would have been more satisfactory outcomes had the drug been continued longer. Saunders[1] reported that some patients required to be on phenelzine for 15 days before responding adequately.

I am using Nardil along with ECT in a number of cases not listed above; it appears to act very satisfactorily, but because of multiple factors playing a part in the recovery, these cases have not been reported in this series.

Comment

The classification of depressive states is almost as complex as the analysis of the drugs used in the treatment of the conditions. Lehman[2] recently pointed out that the approach to the question of depression could be either phenomenological, aetiological, somatotypological, nosological, oecological, or neuropharmacological. A list such as this brings home the formidable difficulties in arriving at any satisfactory classification of depression. For the purpose of this paper and with relatively few cases, categorical complexities had to be avoided. A simple division under 4 self-explanatory headings was therefore used: Endogenous depression (cyclothymic), endogenous depression (hypochondriacal), reactive depression and involutional depression.

In the assessment of the drug's effect, only two determinants were used: *satisfactory*, when the depression lifted and the patient remained affectively well, and *unsatisfactory*, when either the depression remained or treatment had to be discontinued because of side-effects.

DISCUSSION

The neuropharmacological treatment of depression has taken a great step forward in the last 5 years, and Himwich,[3] notes 41 drugs recently brought out for use in mental diseases.

The complexities of the biologic amines are far from being simplified by recent work and there is little point in a detailed discussion of these matters in a short paper dealing with clinical responses. It seems likely, however, that drugs which inhibit MAO lead to an increase in central catechol amines and an improvement in the general responsiveness of the individual.[4]

According to Pletscher and Besendorf,[5] there are two classes of MAO inhibitors: (*a*) Long-acting inhibitors, which are mainly hydrazine derivatives (Nardil falls under this heading), and (*b*) a shorter acting group which includes amphetamine and harmaline. The distribution of MAO in the nervous system generally runs parallel to that of serotonin,[6] which is found in highest concentration in the hypothalamus and brainstem. The puzzles of bound and free serotonin have still to be solved but it appears that MAO inhibitors cause an increase of serotonin in the brain, while reserpine, which has a tranquillizing and sometimes a definite emotionally depressing effect, allows serotonin to be freed and metabolized to 5-hydroxyindoleacetic acid.

Another approach to anti-depressive medications has been taken by Himwich,[7] who has considered them according to their effect on the electroencephalogram as either mesodiencephalic activators or mesodiencephalic blockers and, although there is no published work along these lines with Nardil, the possibilities of combining electrical investigations with biochemical refinements gives great promise for the future of antidepressives. It would seem that phenelzine is a definite step along the road which will lead to adequate control and reversal of depressive states.

ADDENDUM

Since the completion of this article another series of cases of depression has been followed up for a period of 2 months. Of a total of 36 depressive cases 22 made a full and satisfactory recovery without the use of ECT.

I should like to thank Messrs. Warner Pharmaceuticals (Pty.) Ltd. for the generous supply of tablets used in this test.

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